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REVIEW ARTICLE

Necrotising enterocolitis

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Necrotising enterocolitis (NEC) is now the most common acquired gastrointestinal emergency in a neonatal intensive care unit (NICU). The initial clinical manifestations may be indistinguishable from other neonatal infections and NEC is suspected when gastrointestinal signs predominate. These include abdominal distension and tenderness, retention of feeds with ileus, blood in the stool, peritonitis and bowel perforation. Pneumatosis intestinalis (intramural gas) or intrahepatic venous gas are radiological hallmarks of NEC which some authorities (Kliegman & Fanaroff, 1984) require to confirm the diagnosis. In the absence of intramural gas (14% of cases) histopathological examination of tissue collected at the time of surgery or postmortem is necessary to confirm the diagnosis. Necrotising enterocolitis usually affects the terminal ileum and ascending colon although in severe cases the whole bowel may be involved.

It appears that NEC is a disease with multiple causes and multiple contributory factors. Unknown factors alter the gut mucosa directly or indirectly and thus alter the defence mechanism of the gut against infectious agents. If the gut mucosa is damaged feeds are not well tolerated and gas produced by intestinal bacteria may pass through the friable mucosa to become lodged in the submucosa. The friable mucosa also facilitates the absorption of intestinal organisms and/or their toxins leading to further local damage, peritonitis and bacteraemia.

The primary event in the pathogenesis of NEC is generally thought to be an ischaemic insult to the intestine with resulting localized hypoxia. A number of events may lead to ischaemia or hypoxia in the newborn baby especially if pre-term. In addition to intrauterine distress, birth asphyxia, respiratory distress and local trauma resulting from aggressive neonatal care, Lloyd (1969) suggested that newborn babies may exhibit the diving reflex shown by certain mammals in which, during an hypoxic episode, cerebral perfusion is protected at the expense of less vital organs, such as the gut. Experiments by Touloukian *et al.* (1972) and Alward *et al.* (1978) showed a dramatic decrease in mesenteric blood flow in response to

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asphyxia, and in animals killed 2 h after a period of asphyxia intestinal mucosal lesions were observed. Similarly Barlow *et al.* (1974) provoked bloody diarrhoea in rats subjected to profound asphyxia. While many events in the early life of a premature neonate may result in periods of hypoxia or intestinal ischaemia none of the controlled trials have reported an increased incidence of hypoxia among babies who went on to develop NEC (Frantz *et al.*, 1975, Kliegman *et al.*, 1982).

The overall mortality from NEC is in the range 20–40% (Kleigman & Fanaroff, 1984). There is wide variation in reported rates, partly as a result of the definition of NEC. In their study of 64 cases Santulli *et al.* (1975) recorded a 75% mortality.

In an attempt to provide a more uniform system for evaluating cases of NEC and in order to provide a basis for epidemiological studies Bell *et al.*, (1978*b*) proposed three defined stages for NEC according to presenting signs and symptoms. Stage I included those patients with mild signs suspected of having early NEC, but in whom the diagnosis could not be confirmed probably because of early treatment. Patients with confirmatory or severe signs and symptoms of NEC were classified as stages II and III. In the surveillance study carried out by the British Association of Perinatal Paediatrics and the Public Health Laboratory Service Communicable Disease Surveillance Centre (1983) two grades of NEC are recognized. In general these terms corresponded to stages II & III of Bell *et al.* (1978*b*).

Although a condition indistinguishable from NEC has been recognized for more than 150 years it is generally believed that the incidence has increased with the advent of modern neonatal intensive care (Lawrence *et al.*, 1982). NEC predominantly affects premature neonates in intensive care units. There is widespread variation in incidence between and within units. Variation within a unit is due to periodic clusters of cases superimposed upon less frequent endemic cases. The incidence of NEC in the UK is not known, but in the USA the overall incidence among premature babies is quoted as 1–2% increasing to 5% during local outbreaks (Kliegman & Fanaroff, 1981; Brown & Sweet, 1982) and it has been estimated that 2000–4000 newborn infants per year develop NEC (Wilson *et al.*, 1981; Brown & Sweet, 1982). The incidence increases markedly with increasing prematurity and may reach 12% if premature infants who survive until enteric feeds are begun are included. More mature babies are not immune to NEC and 10% cases occur among term neonates (Polin *et al.*, 1976; Kliegman & Fanaroff, 1981). Prior to the development of symptoms 90–95% NEC patients have received human milk or formula feed. In the study by Krousoup (1980) only 3% of 298 NEC patients developed symptoms before their first feed. Intramural gas is not a feature of those cases which develop before the introduction of milk feeds. Early suggestions that human milk protects the infant from NEC have not been borne out by subsequent investigation. The onset of NEC is usually between day 3 and 10 of life but the age at onset may range from 1 to 90 days and there are some

reports of NEC occurring outside the neonatal period (Dagan *et al.*, 1984).

Considerable effort has been made to establish the nature of the initial insult which damages the intestinal mucosa and therefore predisposes a baby to NEC. Fetal hypoxic stress, birth asphyxia, respiratory distress, umbilical arterial catheterisation, overfeeding, exchange transfusions, congenital heart disease, liberation of plasticisers from intravenous equipment, hyperviscosity and specific bacterial and viral pathogens have all been considered. Lake & Walker (1977) proposed that these factors operated by increasing the mucosal permeability of the gut to pathogenic bacteria or their toxins and in early uncontrolled studies many of these factors were implicated in the aetiology of NEC. Subsequent controlled investigations failed to demonstrate any association between NEC and the various high risk factors which had been suggested nor were any differences recognized between NEC babies and other NICU babies matched for gestational age, birthweight and duration of stay in the NICU (Ryder *et al.*, 1980; Stoll *et al.*, 1980; Kliegman *et al.*, 1982; Yu *et al.*, 1984). There still remains no satisfactory unifying explanation for NEC.

The early outbreaks of NEC and the way in which cases clustered lead to the obvious conclusion that NEC represented another manifestation of neonatal sepsis (Kliegman, 1979). The known association between *Clostridium difficile* and pseudomembranous colitis in adults and the finding of this organism in the faeces of neonates suffering from NEC lead to serious consideration that this species of *Clostridium* or clostridia in general might be responsible for NEC. Early workers specifically implicated *C. perfringens* (Kleigman *et al.*, 1979), *C. butyricum* (Howard *et al.*, 1977) and *C. difficile* (Cashore *et al.*, 1981) in the pathogenesis of NEC. Subsequently it has been shown that these organisms are part of the normal neonatal gut flora (Smith *et al.*, 1980; Richardson *et al.*, 1983; Westra-Meijer *et al.*, 1983; Bolton *et al.*, *al.*, 1984). Attempts to implicate clostridial toxin in the pathogenesis of NEC have been equally unrewarding. While some workers (Chang & Areson, 1978; Stoll *et al.*, 1980) have failed to demonstrate toxin in the faeces of symptomatic patients or matched healthy controls, others have described cytopathic toxin as a relatively common finding in the faeces of healthy neonates and infants (Rietra *et al.*, 1978; Richardson *et al.*, 1983). Thomas *et al.* (1984) sought unsuccessfully to show that the concentration of toxin was higher in the faeces of babies with NEC than in asymptomatic controls. They concluded that *C. difficile* was unlikely to be involved in the pathogenesis of NEC. These workers failed also to demonstrate the alpha-toxin of *C. perfringens* in the faeces of 33 babies with NEC, however, for various reasons were this toxin produced locally at the site of a necrotic lesion it may not be detectable in faeces. Viruses (Chany *et al.*, 1982; Mogilner *et al.*, 1983; Rotbart *et al.*, 1983) and coliforms also have been implicated in outbreaks of NEC, but the evidence is unconvincing.

Studies by Frantz *et al.* (1975); Bell *et al.* (1978*a*) and Westra-Meijer *et al.* (1983) suggest the possibility that the isolation of *Klebsiella* spp. from the

faeces of premature neonates may be more closely related to NEC than the isolation of clostridia. These authors all report significantly higher isolation rates for *Klebsiella* spp. in NEC patients than in control groups (*P* values ranging from 0·005 – 0·03). Bell *et al.* (1979) also examined the bowel flora of neonates in relation to the incidence of NEC. They noted a direct relationship between the incidence of NEC and colonisation rates for *Klebsiella* spp. and *Escherichia coli* from the stomach and faeces of babies. They concluded that the variation in incidence of NEC correlates with the predominant bacterial flora in the NICU concerned. Stanley *et al.*, (1977) also reported a decrease in the incidence of NEC coincident with a change in the dominant faecal flora, *Klebsiella* spp. being replaced by *Serratia* spp.

Experimentally, when germfree neonatal animals are contaminated with a single strain of bacteria the organism will populate the gut in high numbers, even if it is not normally part of the gut flora. Lawrence *et al.* (1982) observed enteritis in newborn germ free rats following monoinoculation with *Staph. aureus*, *Staph. epidermidis*, *C. perfringens*, *C. butyricum*, *Bacillus cereus* and *Ps. aeruginosa*, all of which produce an exotoxin. Enteritis did not occur with *Klebsiella* spp. or *E. coli*. The subsequent clinical picture with blood in the faeces and progression to intestinal obstruction was similar to that seen in babies. When neonatal rats were inoculated sequentially with either *Staph. aureus* or *B. cereus* followed 24 h later (before symptoms developed) with *Klebsiella* spp., experimental NEC developed as with *Staph. aureus* or *B. cereus* alone. However, when the animals were killed and the contents of the affected gut examined, *Klebsiella* sp. outnumbered *Staph. aureus* by a factor of 10,000:1. This suggests that the bacteria cultured from clinical cases of NEC might not actually be those that initiate the disease. In contrast to these findings, when healthy control neonatal animals with a normal gut flora were contaminated with *Staph. aureus* etc. they showed no ill effects. Neither did adult animals who, having first been rendered germ free, were then contaminated with a pure culture of an enteritis producing bacterium. Lawrence *et al.* (1982) suggest that neonates in the highly protected environment of a NICU may be in a similar situation to the germ free animal and that heavy colonization of the neonatal gut with one of a number of bacterial strains may lead to gut damage. The development of NEC in babies recently removed from the NICU because of good clinical progress (Stoll *et al.*, 1980) may be considered analagous to the removal of the germ free animal from its isolator.

In view of the experimental work reported by Lawrence *et al.* (1982) caution must be exercised in interpreting cultural findings from cases of NEC for it may be that in neonates as in experimental animals the micro-organisms responsible for NEC may not be present in the faeces. The evidence to date would suggest that NEC represents the common end result of mucosal penetration by one of a range of different bacteria or their toxins and not the effect of a specific bacterium (Thomas, 1982). The case for bacteria having a role in NEC is supported by the finding of elevated levels

of D-lactate in the urine of patients suffering from NEC but not in the urine of healthy controls since only bacteria produce significant amounts of this isomer of lactate (Garcia *et al.*, 1984).

Further support for the role of bacteria in the pathogenesis of NEC comes from the work of Gonzalez-Crussi & Wei Hsueh (1983) who produced ischaemic bowel necrosis in rats by the intra-aortic administration of platelet activating factor and bacterial lipopolysaccharide. Necrotic lesions were not produced at any other sites and neither component produced necrosis when injected alone. The authors suggest the possible involvement of platelet activating factor and lipopolysaccharide in the pathogenesis of NEC and other forms of ischaemic bowel necrosis.

Lawrence *et al.* (1982) propose that the NICU environment itself and the modern aggressive methods of care provided to premature neonates may be responsible for the development of NEC. They suggest that because of the isolation and clinical cleanliness of the unit premature babies are colonized with fewer strains of bacteria. The risk of monocolonization is high and if the organisms involved are toxin producers then the toxic products of bacterial growth can be absorbed through the immature gut wall and lead to intestinal damage—the start of NEC. The widespread use of antibiotics in NICU's may further reduce the range of bacteria with which premature babies may become colonized. In contrast to this situation healthy babies are rapidly colonized by a succession of micro-organisms from their mother and the environment. Factors in the environment of the healthy neonate may contribute also to its resistance to NEC and help it to cope with colonizing bacteria during the first hours of life. Colostrum and human milk contain not only bactericidal and bacteriostatic substances such as lactoferrin and lysozyme but also growth promoting factors which may assist in the rapid colonization of the neonatal gut with a mixed population of non-enteritis producing bacteria.

The hypothesis of Lawrence *et al.* (1982) that NEC is a consequence, possibly an unavoidable consequence, of modern neonatal care is supported by Puri & Guiney (1980) who in a study of NEC in three Dublin hospitals observed 13 cases of NEC in a hospital which took an aggressive approach to the management of low birthweight sick neonates and had a perinatal mortality rate of 15·9/1000. In contrast in two other hospitals where neonatal care was less aggressive there was only one case of NEC during the same 3-year period. The perinatal mortality rates in these hospitals, which delivered a comparable number of babies, were 19·4 and 19·8/1000 respectively.

If colonization of the gut with one of several different bacteria is contributory to the pathogenesis of NEC it is difficult to see how it can be prevented except by employing unrealistic measures of infection control and even then such procedures are only likely to delay the development of NEC until the infant leaves its protective environment. Alternatively artificial gut colonization by organisms such as lactobacilli might be

practicable and protective and the feeding of yoghurt to babies has been proposed.

The characteristic clustering of NEC cases strongly suggests that cross infection is involved in its spread. An outbreak may be contained by appropriate control of infection procedures including isolation of affected babies, cohorting of staff, spacing of incubators, rigid enforcement of hand washing and other control procedures and closing the unit to further admissions. Book *et al.* (1977) reported a significant reduction in the incidence of NEC following the introduction of cross infection control measures and others have reported the control of NEC outbreaks following the introduction of infection control procedures (Powell *et al.*, 1980).

However, Virnig *et al.* (1974) could demonstrate no association between nurse assignment or the location of incubators and the spread of NEC.

It has been suggested (Haley & Bregman, 1982) that the incidence of staphylococcal infection in a neonatal unit goes up during periods of staff shortage, overcrowding or stress. Although these factors have not apparently been investigated in the context of NEC they may possibly contribute to the clustering of cases. Possibly also when the patient/trained staff ratio rises there is an added risk of delay in recognising episodes of neonatal hypoxia which could initiate the sequence of events leading to clinical NEC.

Prophylactic oral aminoglycosides have been used in an attempt to prevent the spread of NEC. Some reports claim that this is a useful practice (Egan *et al.*, 1976; Grylack & Scanlon, 1978) but it is generally held not to be so and is to be discouraged.

While there is an apparent correlation between the introduction of milk feeding and the development of NEC there is no general agreement about the feeding procedures for premature neonates which will decrease the risk of NEC. (Cooke, 1982; Eyal *et al.*, 1982; Kliegman & Fanaroff, 1984).

It is believed that aggressive treatment should be initiated at the first sign of NEC. Umbilical catheters should be removed whenever possible and oral feeding should be stopped. Fluid and electrolyte balances must be maintained through peripheral lines and blood or plasma may be required to maintain blood volume. The rapid progression of NEC and the high incidence of bacteraemia dictate that antimicrobial chemotherapy be initiated early in management. The majority of units in the UK rely on initial treatment with metronidazole, gentamicin together with penicillin or ampicillin on the supposition that anaerobic bacteria may be involved in the necrotic lesion even though coliforms are more frequently isolated from blood cultures. Following the successful use of vancomycin in the treatment of adult *C. difficile* colitis some neonatal units base initial treatment around vancomycin. There now seems little justification for this. Initial therapy may require modification if bacteria are isolated from the blood. Bacteria may be isolated also from peritoneal fluid but Thomas (1982) argued against routine paracentesis because it is difficult to be certain of the origin of any fluid obtained.

Parenteral fluids and feeding are continued for at least 5 days after gastrointestinal function and abdominal X-rays have returned to normal. This is usually 10–21 days after symptoms first appear. Most babies do not require central venous alimentation as peripheral alimentation can usually be maintained for 2–3 weeks. In the absence of bacteraemia or peritonitis antibiotics should continue for 10–14 days except in the mildest (NEC suspected group) of cases.

Intestinal perforation which occurs in up to 30% of cases is probably the most serious complication of NEC and in the majority of cases requires surgical intervention. Surgery has also been advocated when there is a right lower quadrant mass, a persistent dilated loop of bowel, abdominal wall erythema, thrombocytopenia, ascites, acidosis or failure to respond to medical treatment. It is now generally considered that in the absence of intestinal perforation surgery should be avoided (Kosloski & Goldthorn, 1982) and there are reports of successful medical management even in cases of perforation (Reid & Shannon, 1973; Harvey, unpublished communication).

Intestinal strictures may occur in as many as 10% NEC patients. Many centres consider a routine barium enema on NEC patients prior to reintroduction of oral feeds to be unwarranted, however, if abdominal symptoms recur or there is suspicion of abdominal obstruction immediate radiological investigations are essential.

At the present time when there is no identifiable aetiology for NEC and the only recognizable risk factor is prematurity it is difficult to see how this condition can be prevented. However if energetic infection control procedures are introduced immediately the first case is recognized it is probable that spread of the condition can be restricted.

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